37. (Thrice Amended) The composition according to any one of claims 27 or 30-31 wherein the immunogenic portion consists of six immunogenic polypeptides, wherein the polypeptides are an amino-terminal portion of at least one Group A streptococcal M protein.

56. (Twice Amended) The polypeptide according to any one of claims 12 or 27 wherein the immunogenic portion consists of ten immunogenic polypeptides, wherein the polypeptides are an amino-terminal portion of a Group A streptococcal M protein.

REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is respectfully requested. As noted above, Applicant has hereby amended claims 12, 16, 27, 37, and 56 to more clearly define the subject matter encompassed by Applicant's invention. No new matter has been added. Therefore, claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44, and 54-58 are currently pending.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

OBJECTION TO DRAWINGS

In the Office Action dated July 26, 2002, the objection to the drawing made in paragraph 1 of the Office Action mailed May 26, 1999 (Paper No. 11) is maintained for reasons set forth therein. Applicant respectfully submits that formal drawings are provided herewith as requested in the Notice of Draftperson's Patent Drawing Review dated May 21, 1999. Accordingly, Applicant respectfully submits that this ground of objection has been obviated and, therefore, requests that the objection be withdrawn.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

In the Office Action, claims 12, 15, 17, 19, 21, 23, 27, 30-32, 34, 36, 38, 40, 42, 44, 54, 55, 57 and 58 were rejected under 35 U.S.C. §112, first paragraph, for lack of

enablement. More specifically, it is asserted that the specification does not provide enablement for a recombinant fusion polypeptide comprising any two 10 amino acid polypeptides other than the one obtained from Group A streptococcal M protein.

Applicant respectfully traverses this ground of rejection and submits that the disclosure of the instant specification is commensurate in scope with the claims and that no undue experimentation is required to practice the invention. The present invention is directed, in pertinent part for this rejection, to a recombinant fusion polypeptide, comprising (a) a multivalent immunogenic portion wherein the immunogenic portion comprises at least two immunogenic polypeptides from Group A streptococcal M protein, the polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and (b) a carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion. Thus, a person having ordinary skill in the art at the time of filing would have known how to identify and use immunogenic polypeptides according to the instant invention by mere routine experimentation. Nevertheless, however, merely to expedite prosecution of the subject application, Applicant has hereby amended claims 12 and 27 to recite "the immunogenic portion comprises at least two immunogenic polypeptides from Group A streptococcal M protein", as suggested by the Examiner.

Accordingly, Applicant respectfully submits that the claims satisfy the requirements of 35 U.S.C. §112, first paragraph and, therefore, requests that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

In the Office Action, claims 16, 37, 56 and 57 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. Specifically, it is alleged that the phrase "M protein" is vague and indefinite because it is unclear from which organism the claimed "M protein" originates.

Applicant respectfully traverses this ground of rejection. Applicant respectfully submits that the claims' recitation of the term "M protein" is clearly defined in the specification

and has a meaning that is clear to a person skilled in the art (*see, e.g.*, specification at page 6, 11-13 and 27-29), which is therefore definite within the meaning of Section 112, second paragraph. Nevertheless, however, merely to expedite prosecution of the subject application, Applicant has amended claims 16, 37, and 56 to recite "Group A streptococcal M protein."

Accordingly, Applicant respectfully submits that the claims satisfy the requirements of 35 U.S.C. §112, second paragraph and, therefore, requests that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 103(a)

In the Office Action, claims 12, 15, 27 and 36 were rejected under 35 U.S.C. §103(a) as obvious over Hruby *et al.* (*Proc. Nat'l Acad. Sci. USA 88*:3190, 1991) in view of Marston and Hartley (*Methods in Enzymology, Guide to Protein Purification*. Deutscher (Ed.), Vol. 182, Section 20, pages 264-276, 1991). It is alleged that it would have been obvious for a person having ordinary skill in the art to express the recombinant CRR protein of Hruby *et al.* as a multivalent fusion polypeptide according to Marston and Hartley to arrive at the instant invention with a reasonable expectation of success. It is further alleged that a skilled artisan would have been motivated to produce the instant invention for the expected benefit of facilitating the efficient purification of a fusion polypeptide given that fusion polypeptides are routinely used to purify polypeptides, as taught by Marston and Hartley.

Applicant respectfully traverses this ground of rejection. Applicant respectfully submits that Hruby *et al.* and Marston and Hartley, taken alone or in combination, fail to teach or suggest the claimed invention and, furthermore, would not have motivated a person having ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success. The present invention is directed, in pertinent part for this rejection, to a recombinant fusion polypeptide, comprising (a) a multivalent immunogenic portion wherein the immunogenic portion comprises at least two immunogenic polypeptides from Group A streptococcal M protein, the polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and (b) a carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the

immunogenic portion. As discussed in more detail below, Applicant respectfully submits that a *prima facie* case of obviousness has not been established by the Patent Office because neither Hruby *et al.* nor Marston and Hartley individually or in combination teach or suggest every limitation of the instant claims. In particular, these references taken together fail to teach or suggest a fusion polypeptide comprising a *multivalent* immunogenic portion having at least two immunogenic polypeptides and a carboxy-terminal polypeptide that is a *reiteration* of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion.

Hruby *et al.* merely teach the construction of tandem in-frame repeats of the C-repeat region (CRR) from streptococcal M6 protein imbedded in and fused to the thymidine kinase of vaccinia virus (*see* Hruby *et al.* at page 3192, Figure 1B). Hence, as noted in the Office Action, Hruby *et al.* fail to teach or suggest a fusion polypeptide having a multivalent immunogenic portion. In addition, Applicant respectfully submits that, contrary to the assertion in the Office Action, Hruby *et al.* fail to teach or suggest a fusion polypeptide having a carboxy-terminal polypeptide that is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion. The Hruby *et al.* three-copy CRR tandem repeat has fused at the carboxyl terminus a portion of the vaccinia virus thymidine kinase (TK) gene, which is expressed as a fusion having the structure $[CRR]_n$-TK (*see* Hruby *et al.* at page 3192, Figure 1B and at page 3193, first column, lines 1-14). That is, the carboxy-terminal polypeptide is not a reiteration of an immunogenic polypeptide from the immunogenic portion. Thus, Hruby *et al.* concededly fail to teach or suggest a recombinant fusion polypeptide according to the instant invention.

Furthermore, Applicant respectfully submits that the deficiencies of Hruby *et al.* are not remedied by the disclosure of Marston and Hartley. Marston and Hartley merely present general methods for use in isolating and solubilizing protein aggregates arising from over-expression of recombinant genes. Applicant respectfully submits that Marston and Hartley is a general reference regarding solubilization of highly expressed proteins and, therefore, provides no teaching or suggestion pertaining to the claimed fusion polypeptides. Consequently, Marston and Hartley are silent with regard to Group A streptococcal M protein, immunogenic portion having immunogenic polypeptides, a carboxy-terminal polypeptide that is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion, much less a

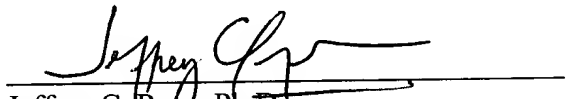
multivalent fusion polypeptide capable of eliciting an immune response against Group A Streptococci. Hence, Marston and Hartley fail to teach or suggest a recombinant fusion polypeptide according to the instant invention.

Additionally, Applicant respectfully submits that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g., In re Mills*, 16 USPQ2d 1430, Fed. Cir. 1990; *In re Fritch*, 23 USPQ2d 1780, Fed. Cir. 1992). Applicants note that the Patent Office has the burden to clearly articulate what portions of Marston and Hartley and Hruby *et al.* provide the alleged motivation or suggestion to combine these references, which the instant Office Action fails to articulate. Thus, Marston and Hartley alone, or taken in combination with Hruby *et al.*, fail to render the claimed invention obvious.

Applicant, therefore, respectfully submits that the Patent Office has not set forth a *prima facie* case of obviousness because the cited references, taken alone or in combination, fail to teach every limitation of the instant invention and fail to provide motivation for a person having ordinary skill in the art to modify or combine the prior art teachings to arrive at the claimed invention with a reasonable expectation of success. Accordingly, applicants respectfully request that this ground of rejection be withdrawn.

All of the claims pending in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions prior to allowance of this matter.

Respectfully submitted,
Seed Intellectual Property Law Group PLLC



Jeffrey C. Pepe, Ph.D.
Registration No. 46,985

Enclosures: 9 sheets of Formal Drawings (Figures 1 – 7B)

Phone: (206) 622-4900
Fax: (206) 682-6031

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 17 of page 3 has been amended as follows:

Figure 2 is a SDS-polyacrylamide gel electrophoresis of the purified hexavalent protein stained with ~~coomassie~~ Coomassie™ blue. Computer-assisted image analysis of the stained protein bands indicated that the hexavalent protein (M.W. 45 kDa) accounted for ~~90.3%~~ 86% to 89% of the total protein in the sample.

In the Claims:

Claims 12 16, 27, 37, and 56 have been amended as follows:

12. (Thrice Amended) A recombinant fusion polypeptide, comprising:

(a) a multivalent immunogenic portion wherein the immunogenic portion comprises at least two immunogenic polypeptides from Group A streptococcal M protein, the polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(b) a carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion.

16. (Thrice Amended) The polypeptide according to claim 12 wherein the immunogenic portion consists of six immunogenic polypeptides, wherein the polypeptides are an amino-terminal portion of at least one Group A streptococcal M protein.

27. (Thrice Amended) A composition for promoting an immune response against Group A Streptococci, comprising:

(a) a recombinant fusion polypeptide, comprising:

(i) a multivalent immunogenic portion wherein the immunogenic portion comprises ~~at least two immunogenic~~ polypeptides from Group A streptococcal M protein, the polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(ii) a carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion; and

(b) a pharmaceutically acceptable excipient or diluent.

37. (Thrice Amended) The composition according to any one of claims 27 or 30-31 wherein the immunogenic portion consists of six immunogenic polypeptides, wherein the polypeptides are an amino-terminal portion of at least one Group A streptococcal M protein.

56. (Twice Amended) The polypeptide according to any one of claims 12 or 27 wherein the immunogenic portion consists of ten immunogenic polypeptides, wherein the polypeptides are an amino-terminal portion of a Group A streptococcal M protein.

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